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YIF1B-Related Neurodevelopmental Disorder

Synonym: Kaya-Barakat-Masson Syndrome (KABAMAS)

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Summary

Clinical characteristics

YIF1B-related neurodevelopmental disorder (*YIF1B*-NDD) is characterized by severe-to-profound developmental delay / intellectual disability with variable motor abnormalities including axial hypotonia, peripheral hypertonia, dystonia, and dyskinesia; absence of speech in most individuals or very limited speech subject to regression; feeding difficulties; seizures; postnatal microcephaly with nonspecific brain MRI abnormalities; and ophthalmologic involvement (strabismus, nystagmus, optic atrophy, and cortical blindness). Some individuals have hypoventilation.

Diagnosis/testing

The diagnosis of *YIF1B*-NDD is established in a proband with suggestive findings and biallelic pathogenic variants in *YIF1B* identified by molecular genetic testing.

Management

Treatment of manifestations: Developmental and educational support; feeding therapy; gastrostomy tube placement if required for persistent feeding issues; standardized treatments for movement disorder and seizures by an experienced neurologist; treatment per ophthalmologist for refractive errors and strabismus; low vision services as needed; consider ventilation therapy when hypoventilation becomes evident; social work and family support.

Surveillance: Monitor developmental progress, educational needs, growth, nutritional status, safety of oral intake, and changes in seizures at each visit; assess for any new manifestations including seizures, changes in tone, movement disorders, or manifestations of central hypoventilation at each visit; ophthalmology evaluation per treating ophthalmologist; behavioral assessment annually.

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Genetic counseling

YIF1B-NDD is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *YIF1B* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once the *YIF1B* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal/preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

YIF1B-related neurodevelopmental disorder (*YIF1B*-NDD) **should be considered** in probands with the following clinical, imaging, and family history findings.

Clinical findings

- Severe-to-profound developmental delay; most individuals do not obtain any developmental milestones.
- Severe-to-profound intellectual disability, with no speech development or limited speech with subsequent regression
- Generalized axial hypotonia of infancy and concurrent peripheral hypertonia
- Infant feeding difficulties
- Movement disorders, including dystonia and dyskinesia or tremors
- Epilepsy, varying from myoclonic seizures to generalized tonic-clonic seizures and infantile spasms
- Neurobehavioral/psychiatric manifestations including autism spectrum disorder and anxiety
- Postnatal microcephaly
- Ophthalmologic involvement, including strabismus, nystagmus, optic atrophy, and cortical blindness
- Hypoventilation and ventilation dependency in the presence of brain stem atrophy

Imaging findings on brain MRI. Nonspecific findings include white matter and myelination abnormalities, corpus callosum hypoplasia, cerebellar atrophy and parenchymal volume loss, cerebellar hypoplasia, and pons and brain stem atrophy (see Figure 1).

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *YIF1B*-NDD **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *YIF1B* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of biallelic *YIF1B* variants of uncertain significance (or of one known *YIF1B* pathogenic variant and one *YIF1B* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

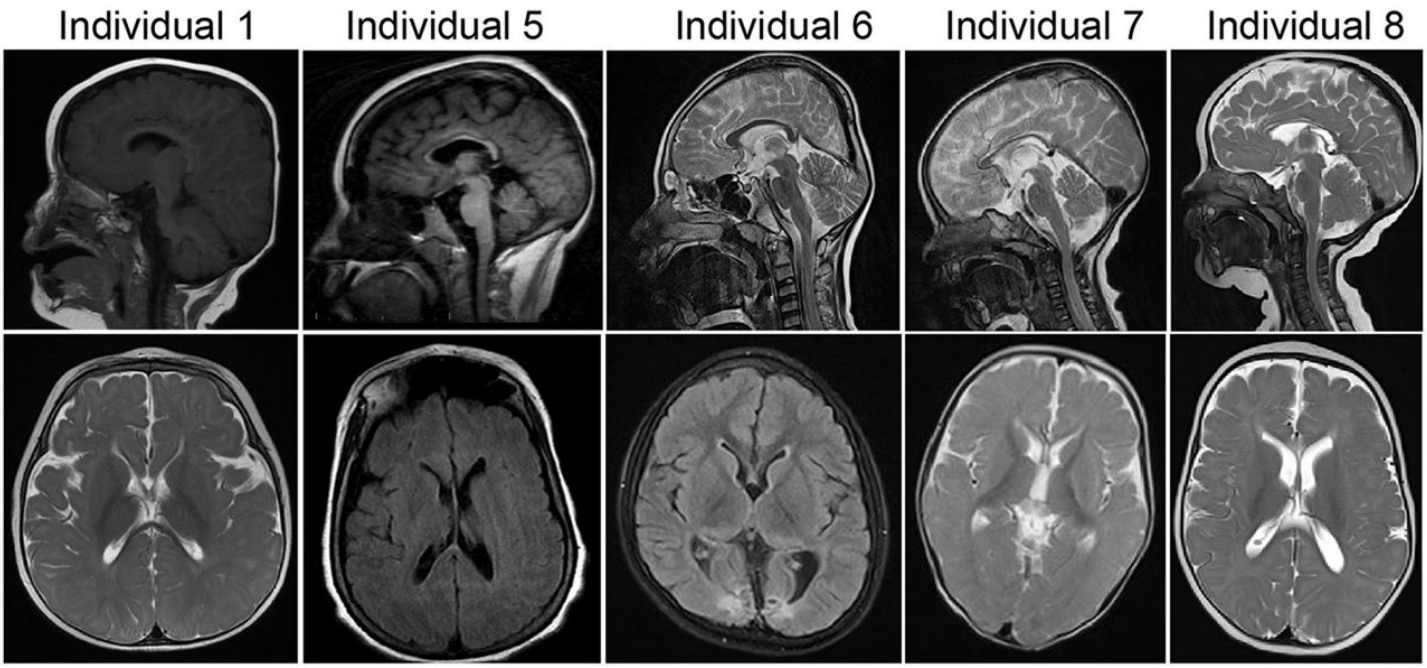

Figure 1. T_1- and T_2-weighted brain MRI images of Individuals 1 and 5-8 in sagittal and axial planes. Note the various degrees of cerebral atrophy, cerebellar hypoplasia, thin corpus callosum, and white matter abnormalities.

Reproduced with permission from Medico Salsench et al [2021]

Note: Single-gene testing (sequence analysis of *YIF1B* followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

Option 1

An intellectual disability, epilepsy, or movement disorder multigene panel that includes *YIF1B* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. To date, the majority of *YIF1B* pathogenic variants reported (e.g., missense, nonsense) are within the coding region and are likely to be identified on exome sequencing. Additionally, two splice site pathogenic variants have been identified using exome sequencing.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *YIF1B*-Related Neurodevelopmental Disorder

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
YIF1B	Sequence analysis [3]	96% [4]
	Gene-targeted deletion/duplication analysis [5]	4% [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. To date, 24/25 reported individuals had biallelic pathogenic variants identified using exome sequencing [AlMuhaizea et al 2020, Diaz et al 2020, Medico Salsench et al 2021, Sanri et al 2023]. A single affected individual had a larger deletion that included *YIF1B* that was identified by genome sequencing [Medico Salsench et al 2021].
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.

Clinical Characteristics

Clinical Description

YIF1B-related neurodevelopmental disorder (*YIF1B*-NDD) is characterized by severe-to-profound developmental delay / intellectual disability with variable motor abnormalities including axial hypotonia, peripheral hypertonia, dystonia, and dyskinesia; absence of speech in most individuals or very limited speech subject to regression; feeding difficulties; seizures; postnatal microcephaly with nonspecific brain MRI abnormalities; and ophthalmologic involvement (strabismus, nystagmus, optic atrophy, and cortical blindness). Some individuals have hypoventilation. To date, 25 individuals have been identified with biallelic pathogenic variants in *YIF1B* [AlMuhaizea et al 2020, Diaz et al 2020, Medico Salsench et al 2021, Sanri et al 2023]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. *YIF1B*-Related Neurodevelopmental Disorder: Frequency of Select Features

Feature	Proportion of Persons w/Feature [1]	Comment
Developmental delay	24/24	Severe to profound
Generalized hypotonia of infancy	20/24	
Intellectual disability	24/24	Severe to profound
Peripheral spasticity & hyperreflexia	22/23	
Infant feeding difficulties	20/24	
Dystonia	12/24	
Dyskinesia or tremor	9/21	
Epilepsy	15/23	Myoclonic, generalized tonic-clonic, & infantile spasms
Microcephaly	16/24	Postnatal onset is most common.
Strabismus	11/19	
Nystagmus	5/20	

Table 2. continued from previous page.

Feature	Proportion of Persons w/Feature [1]	Comment
Optic atrophy	2/21	
Central hypoventilation	6/19	When brain stem is affected
Premature death	5/25	Death occurred before age 2 yrs in 5 persons.

Based on AlMuhaizea et al [2020], Diaz et al [2020], Medico Salsench et al [2021], Sanri et al [2023]
1. Not all features have been reported for all currently known 25 affected individuals.

Developmental delay. All individuals with *YIF1B*-NDD presented with severe-to-profound developmental delay, evident in the first month of life [AlMuhaizea et al 2020, Diaz et al 2020, Medico Salsench et al 2021, Sanri et al 2023]. Normal developmental milestones were most often not achieved. Severe axial hypotonia was seen in most affected individuals, with concurrent peripheral hyperreflexia and spasticity. Head control was only achieved in 5/24 individuals, all of whom had biallelic missense variants; individuals with protein-truncating variants did not achieve head control. Likewise, sitting (4/24), standing (2/24), and walking (2/24) were only observed in individuals with *YIF1B* missense variants. No speech development occurred in individuals with biallelic *YIF1B* protein-truncating variants (0/18), with limited speech development only in 4/6 individuals with biallelic *YIF1B* missense variants; subsequent progressive loss of speech was observed in 3/4 individuals. Feeding problems and difficulties in swallowing occurred in 20/24 individuals early in life, often requiring tube feeding.

Intellectual disability. Although for the majority of affected individuals currently no formal IQ testing results are available, based on clinical estimates the level of intellectually disability of all affected individuals is in the severe-to-profound range [AlMuhaizea et al 2020, Diaz et al 2020, Medico Salsench et al 2021, Sanri et al 2023].

Movement disorders observed in *YIF1B*-NDD include dystonia and dyskinesia or tremor [AlMuhaizea et al 2020, Diaz et al 2020, Medico Salsench et al 2021, Sanri et al 2023]. For those few individuals for which detailed information is available, movement disorders had an onset around age two to three years with the development of choreiform limb movements, which evolved into axial and limb dystonia with dyskinesia by age four to eight years [AlMuhaizea et al 2020]. In those individuals, dystonia was unresponsive to levodopa or carbidopa but partially improved on trihexyphenidyl [AlMuhaizea et al 2020].

Epilepsy. Seizures occurred in 15/23 affected individuals, and included myoclonic, generalized tonic-clonic, and infantile epileptic spasms of variable degrees of severity [AlMuhaizea et al 2020, Diaz et al 2020, Medico Salsench et al 2021, Sanri et al 2023]. Most seizures had onset before age two years, with EEGs showing frequent multifocal and epileptiform discharges and abnormal background indicating diffuse dysfunction. For some individuals, seizure control could be achieved using phenobarbital, levetiracetam, and valproate, whereas others presented with medically refractory generalized epilepsy.

Growth. Growth parameters at birth were normal for those individuals for which information is available. Postnatal microcephaly occurred in 16/24 individuals. Currently, information on postnatal growth and weight is sparse, although a few individuals have been reported to present with poor weight gain and growth deficiency [Diaz et al 2020, Sanri et al 2023].

Ophthalmologic involvement included strabismus, nystagmus, and optic atrophy. Cataract or retinal involvement have not been reported. Cortical blindness was reported in one individual.

Central hypoventilation has been observed in 6/19 reported individuals and seems to be correlated with the level of brain stem atrophy [AlMuhaizea et al 2020, Diaz et al 2020, Medico Salsench et al 2021, Sanri et al 2023]. At least three individuals became ventilation dependent.

Neurobehavioral/psychiatric manifestations. Autism spectrum disorder and autistic behaviors have been reported in 4/14 individuals [AlMuhaizea et al 2020, Diaz et al 2020, Medico Salsench et al 2021, Sanri et al 2023]. Anxiety and aggression have been reported in a single individual [Diaz et al 2020].

Facial features. No consistent recognizable facial features have been reported in individuals affected with *YIF1B*-NDD [AlMuhaizea et al 2020, Diaz et al 2020, Medico Salsench et al 2021, Sanri et al 2023] (see Figure 2).

Prognosis. Premature death (before age 2 years) has been reported in five individuals, all with protein-truncating variants. The precise cause of death has not been reported.

Three individuals were older than age 25 years (the oldest reported individual was age 37 years) at the time of publication, demonstrating that survival into adulthood is possible [Diaz et al 2020, Medico Salsench et al 2021].

Genotype-Phenotype Correlations

Although the number of reported individuals with *YIF1B*-NDD is small (n=25) and the overall phenotype of this disorder is profound to severe, the phenotype of individuals with biallelic protein-truncating *YIF1B* variants tends to be more severe compared to that of individuals with biallelic missense variants [Medico Salsench et al 2021]. Limited developmental milestones – including limited speech development (4/24), head control (5/24), and capacity to sit (4/24), stand (2/24), and walk (2/24) – were only observed in individuals with biallelic missense variants. This might be due to residual activity of YIF1B in those with missense variants compared to protein-truncating variants [Medico Salsench et al 2021].

Prevalence

To date, 25 individuals with *YIF1B*-NDD have been reported in the medical literature [AlMuhaizea et al 2020, Diaz et al 2020, Medico Salsench et al 2021, Sanri et al 2023]. As expected for an autosomal recessive disorder, the majority of affected individuals are offspring of consanguineous parents, with at least 15 reported individuals having consanguineous parents and homozygous variants. At least two pathogenic variants have been observed recurrently, possibly indicating founder variants: c.598G>T (p.Glu200Ter) has been identified in individuals of Somali descent, and c.186dupT (p.Ala63fs) has been identified in individuals of Arabic descent.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *YIF1B*.

Differential Diagnosis

The phenotypic features associated with *YIF1B*-related neurodevelopmental disorder are not sufficient to diagnose this condition clinically. All disorders with severe intellectual disability and/or epilepsy with or without other distinctive findings (including movement disorders) should be considered in the differential diagnosis. See OMIM Phenotypic Series for genes associated with the following:

- Autosomal dominant intellectual developmental disorders
- Autosomal recessive intellectual developmental disorders
- Nonsyndromic X-linked intellectual developmental disorders
- Syndromic X-linked intellectual developmental disorders
- Developmental and epileptic encephalopathy

Figure 2. Images of Individuals 4–7 and 8 at ages 1 year, 27 years, 7.5 years, 11 months, and 4.5 years, respectively. No consistent dysmorphic features were observed. Note the neurologic posture in Individuals 4, 5, and 7.

Reproduced with permission from Medico Salsench et al [2021]

Management

No clinical practice guidelines for *YIF1B*-related neurodevelopmental disorder (*YIF1B*-NDD) have been published. In the absence of published guidelines, the following recommendations are based on the authors' personal experience managing individuals with this disorder.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *YIF1B*-NDD, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. *YIF1B*-Related Neurodevelopmental Disorder: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Gastrointestinal/ Feeding	• Gastroenterology / nutrition / feeding team eval • Growth assessment	• To incl eval of aspiration risk & nutritional status • Consider eval for gastrostomy tube placement in persons w/ dysphagia &/or aspiration risk.
Neurologic	Neurologic eval	• Assess for movement disorder & signs of hypoventilation. • Assess muscle tone. • Consider EEG if seizures are a concern. • Consider brain MRI if not performed previously.
Eyes	Ophthalmologic eval	To assess for reduced vision, abnormal ocular movement, best corrected visual acuity, refractive errors, strabismus, & more complex findings (e.g., cortical blindness) that may require referral for subspecialty care &/or low vision services

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Neurobehavioral/ Psychiatric	Neuropsychiatric eval	For persons age >12 mos: screening for concerns incl findings suggestive of ASD, anxiety, &/or aggression
Genetic counseling	By genetics professionals [1]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of *YIF1B*-NDD to facilitate medical & personal decision making
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement for parental support • Home nursing referral

ASD = autism spectrum disorder; MOI = mode of inheritance; *YIF1B*-NDD = *YIF1B*-related neurodevelopmental disorder
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 4).

Table 4. *YIF1B*-Related Neurodevelopmental Disorder: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability / Neurobehavioral issues	See Developmental Delay / Intellectual Disability Management Issues.	
Feeding issues / Poor weight gain	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study when showing clinical signs or symptoms of dysphagia
Movement disorder	Consider standardized treatments for movement disorders by experienced neurologist.	Individual case reports indicate that levodopa or carbidopa did not improve movement disorders, while partial improvement was obtained using trihexyphenidyl. [1] However, there is no substantial evidence for the efficacy of this treatment in this disorder.
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [2]
Eyes	Treatment per ophthalmologist	For refractive errors, strabismus
	Low vision services	• Children: through early intervention programs &/or school district • Adults: low vision clinic &/or community vision services / OT / mobility services
Central hypoventilation	Consider ventilation therapy if hypoventilation becomes evident.	Consider referral to ventilation specialist.

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	Ongoing assessment of need for palliative care involvement &/or home nursing

ASM = anti-seizure medication; OT = occupational therapy

1. AlMuhaizea et al [2020]

2. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the US; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Neurobehavioral/Psychiatric Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 5 are recommended.

Table 5. *YIF1B*-Related Neurodevelopmental Disorder: Recommended Surveillance

System/Concern	Evaluation	Frequency
Development	Monitor developmental progress & educational needs.	At each visit
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations such as seizures, changes in tone, movement disorders, or manifestations of central hypoventilation.	
Eyes	Evaluate for refractive error, strabismus, nystagmus, & other signs of visual dysfunction	Per treating ophthalmologist
Neurobehavioral/ Psychiatric	Assessment for ASD, anxiety, & aggression	Annually

ASD = autism spectrum disorder

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

YIF1B-related neurodevelopmental disorder (*YIF1B*-NDD) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for a *YIF1B* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *YIF1B* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;

- Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *YIF1B* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. To date, individuals with *YIF1B*-NDD are not known to reproduce.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *YIF1B* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *YIF1B* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to the parents of affected children.
- It is appropriate to offer *YIF1B* molecular genetic testing to the reproductive partners of individuals known to be heterozygous for a *YIF1B* pathogenic variant, particularly if consanguinity is likely.

Prenatal Testing and Preimplantation Genetic Testing

Once the *YIF1B* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  aaidd.org
- **American Epilepsy Society**
  aesnet.org
- **Canadian Epilepsy Alliance**

Canada
Phone: 1-866-EPILEPSY (1-866-374-5377)
canadianepilepsyalliance.org

- **CDC - Child Development**
  Phone: 800-232-4636
  Developmental Disability Basics
- **Epilepsy Foundation**
  Phone: 800-332-1000; 866-748-8008
  epilepsy.com
- **MedlinePlus**
  Intellectual Disability
- **VOR: Speaking out for people with intellectual and developmental disabilities**
  Phone: 877-399-4867
  Email: info@vor.net
  vor.net

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. YIF1B-Related Neurodevelopmental Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
YIF1B	19q13.2	Protein YIF1B	YIF1B	YIF1B

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for YIF1B-Related Neurodevelopmental Disorder (View All in OMIM)

619109	YIP1-INTERACTING FACTOR HOMOLOG B, MEMBRANE-TRAFFICKING PROTEIN; YIF1B
619125	KAYA-BARAKAT-MASSON SYNDROME; KABAMAS

Molecular Pathogenesis

YIF1B encodes YIF1B, a transmembrane protein involved in anterograde protein trafficking from the endoplasmic reticulum to the cell membrane and in the architecture and morphology of the Golgi apparatus. Furthermore, YIF1B interacts with the C terminus of the serotonin receptor HTR1A, where it is proposed to play a role in the transient intracellular trafficking and modulation of 5-HT1AR transport to dendrites in the central nervous system [Carrel et al 2008]. In addition, functional analysis has revealed that YIF1B is involved in lysosomal targeting of ABCB9 (also known as TAPL) [Graab et al 2019] and interacts with RAB6A, a recycle trafficking protein [Al Awabdh et al 2012].

Although the precise molecular mechanisms underlying *YIF1B*-related neurodevelopmental disorder (*YIF1B*-NDD) are not yet fully elucidated, functional studies point to disturbed function of protein trafficking, dysfunction of the Golgi apparatus, and aberrant protein interactions with abnormal YIF1B [Diaz et al 2020, Medico Salsench et al 2021]. In addition to Golgi dysfunction, endoplasmic reticulum morphology and primary cilium integrity are disturbed in the absence of Yif1b, leading to neuronal reduction, neuronal death, and

alterations of myelination of the motor cortex, causing cerebellar atrophy and enlargement of the ventricles in the Yif1b knockout mice [Diaz et al 2020]. In vitro experiments in human cells with mutated YIF1B (due to either protein-truncating or missense variants) show altered subcellular localization and reduced colocalization with known interacting proteins, including TAPL and RAB6A, indicating reduced functionality compared to wild type YIF1B [Medico Salsench et al 2021].

Mechanism of disease causation. Loss of function. The spectrum of *YIF1B* pathogenic variants is suggestive of loss of function as the underlying disease mechanism, with the majority of currently identified pathogenic variants being biallelic, protein-truncating loss-of-function variants. Missense variants tend to be localized in or close to the transmembrane domains, affecting highly conserved residues, and have been shown to negatively impact YIF1B function.

Table 6. *YIF1B* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment
NM_001039672.3 NP_001034761.1	c.598G>T	p.Glu200Ter	Possible founder pathogenic variant in persons of Somali descent
	c.186dupT	p.Ala63fs	Possible founder pathogenic variant in persons of Arabic descent

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

Author Notes

Dr Tahsin Stefan Barakat is a clinical geneticist and experimental biologist with broad clinical and research interests in neurodevelopmental disorders. The Barakat laboratory aims to decipher novel mechanisms of neurodevelopmental disorders and develop novel therapies based on this knowledge.

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Dr TS Barakat (t.barakat@erasmusmc.nl) is actively involved in clinical research regarding individuals with *YIF1B*-NDD and would be happy to communicate with persons who have any questions regarding diagnosis of *YIF1B*-NDD or other considerations.

Contact Dr TS Barakat to inquire about review of *YIF1B* variants of uncertain significance.

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